FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number: 141-053

Sponsor: Pfizer Inc
235 East 42nd St.
New York, NY 10017

Generic Name: carprofen

Trade Name: RIMADYL®

Marketing Status: Rx

II. INDICATIONS FOR USE

RIMADYL® is indicated for the relief of pain and inflammation in dogs. RIMADYL® was shown to be clinically effective for the reflief of signs associated with osteoarthritis in dogs.

III. DOSAGE FORM, ROUTES OF ADMINISTRATION AND RECOMMENDED DOSAGE

A. Dosage Form: RIMADYL® is available as 25, 75, and 100 mg scored caplets.

B. Route of Administration: Oral

C. Recommended Dosage: The recommended dosage of Rimadyl® for oral administration in dogs is 1 mg/lb body weight twice daily. Caplets are scored and dosage should be calculated in half-caplet increments.

IV. EFFECTIVENESS

A. PIVOTAL STUDIES

1. **Rimadyl® (carprofen) dose titration study in dogs**
(Report No.GCR N-127594)

a. Type of Study: Dose Determination

b. Investigator: Dr. A. Joseph Threlkeld
Dr. R. Shapiro
Department of Physical Therapy
University of Kentucky
Lexington, KY 40506

c. General Design:

i. Purpose: The objective of the study was to determine the clinically effective dose of Rimadyl® (carprofen) for relief of signs associated with osteoarthritis in dogs.

ii. Test Animals: Thirty-five dogs used to evaluate carprofen were distributed evenly among treatments and sex. The dogs ranged in age from 9 to 12 months and in weight from 18.5 to 35 lb.

iii. Control Drug: Placebo (similar to other treatments except for the omission of the active ingredient).

iv. Dosage Form: The caplets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dosages used: Carprofen: 0, 1, 2 , 3 and 4 mg/lb b.w. daily

vii: Test Duration: Approximately 6 weeks

viii: Parameters Measured: Improvement in the dogs' gait following surgically induced arthritis of the stifle joint was statistically evaluated using Motion Analysis (Kobluk, et. al., 1989, Proced. 34th Ann. Meet. AAEP, pp 135-148). Range of motion was measured for the affected hip, knee and hock.

A pre-surgical evaluation was performed on each dog to determine the general health of the test animals (complete blood count and serum chemistry profile), an examination for the absence of pre-existing articular diseases (survey radiographs of both stifles), and a graded lameness exam and gait analysis in order to determine a baseline for normal limb movement for each test subject. Experimental surgery was performed on Day 1 of the protocol. A post-surgical examination, that included survey radiographs of the stifles to demonstrate the presence of osteoarthritis and a graded lameness exam and gait analysis to quantitate the pre-treatment lameness, was performed on Day 28.

On Day 36, following eight days of therapy, a post-treatment evaluation was conducted which included a lameness examination and gait analysis in order to quantitate the lameness after treatment. A complete blood count and serum chemistry profile were also conducted.

d. Results: The surgery was shown to produce signs of osteoarthritis in the dogs, with varying degrees of lameness.

The parameters measured from the treadmill for analysis were total range of angular excursion of the left hip in flexion, total range of angular excursion of the left knee in flexion, total range of angular excursion of the left hip in abduction, and total range of vertical excursion of the tibiotarsal joint. The vertical excursion parameter, as measured at the distal tibia, quantitates the vertical lift of the tibiotarsal joint. This motion parameter was determined to be the most sensitive measure of carprofen effect. Individual animals compensate for a weight-bearing knee injury by using varying alterations to gait, such as adjustments to angular movements of the stifle and coxofemoral joints, or tilt of the pelvis. The gait is a complex composite of each of these movements, as well as others. The angular parameters individually and cumulatively result in a change in the vertical displacement of the hock. The vertical excursion of the tibiotarsal joint parameter, therefore, reflects the cumulative effect of the lameness seen.

The mean values for the primary response variable, vertical excursion of the tibiotarsal joint, decreased following surgery for all treatment groups, i.e., dogs did not lift the affected leg as high during their strides. Carprofen administration at daily doses of $\geq$ 2 mg/lb for eight days caused an increase in the vertical excursion, as shown in Table 1. T-test comparisons of least squares means of the primary response variable, vertical excursion of the distal tibia, showed that daily doses of 2, 3, and 4 mg/lb were each significantly different ($p<.05$) from the placebo. The 1 mg/lb dose did not produce a significant difference from placebo. Linear plateau modeling confirmed 2 mg/lb as the minimum effective daily dose.

Table 1
Effects of Various Doses of Carprofen on Mean Post-treatment Vertical Excursion of the Tibiotarsal Joint.

Daily Dose (mg/lb)	Vertical Excursion Of The Tibiotarsal Joint L. S. Means (in)	P-value
0	1.37	--
1	1.29	0.3838
2	1.83	0.0428*
3	1.82	0.0452*
4	2.42	0.0005*

* Significantly different from placebo, $P<0.05$.

Subjective lameness examinations did not detect statistically significant changes in the post-treatment conditions of the dogs in this model.

e. Statistical Analysis: A paired t-test between pre-surgery and post-surgery measurements for each of the variables was used to test the surgery effect. To evaluate the drug effect, the Analysis of Variance model included handling group, treatment, and post-surgical value (as a covariate). A family of Anderson & Nelson linear plateau models were fitted to the least squares means obtained from the above model to determine the dose response relationship if the dose effect was significant. Each of the non-zero doses were compared with the placebo using a one-sided t-test at alpha = .05 to identify the minimum effective dose.

f. Conclusions: The minimum effective dose for carprofen was determined to be 2 mg/lb of body weight.

g. Adverse Reactions: No adverse reactions to the administration of carprofen were reported.

2. **Rimadyl® (carprofen) clinical field trials at small animal clinics**
(Report No. CR-G-5001-94)

a. Type of Study: Multicentered Clinical Field Study

b. Investigators:

Name	Cases
Dr. Mark Frost Herchel Animal Clinic Jacksonville, FL	38
Dr. Robert McLain Addison Animal Hospital Addison, IL	40
Dr. Peter Eeg Peachtree Veterinary Clinic Beallsville, MD	23
Dr. John Donecker Reidsville Veterinary Hospital Reidsville, NC	39
Dr. Robert Bialt Glen Animal Hospital Sea Cliff, NY	5

Name	Cases
Dr. Donna Rauch Vernon Hills Animal Hospital Mundelein, IL	18
Dr. Robert Reschke Worth Animal Hospital Palos Hills, IL	19
Dr. Susan Anway Perinton Animal Hospital Victor, NY	19
Dr. Richard Benjamin Berkeley Dog and Cat Hospital Berkeley, CA	7
Dr. Robin Holtsinger University of Florida Gainesville, FL	19

c. General Design:

i. Purpose: The objective of the study was to evaluate, under field conditions, the efficacy and safety of Rimadyl® (carprofen) for the relief of the acute signs associated with canine osteoarthritis.

ii. Test Animals: Two hundred twenty-seven cases were used to evaluate carprofen and 107 of them were treated with carprofen while 120 were treated with placebo. Dogs presenting in the course of clinical practice with an osteoarthritic condition were admitted to the study. Dogs were excluded from enrollment if any of the following were present: pregnancy; known bleeding disorders; treatment with topical or systemic anti-inflammatory drugs or antibiotics; intra-articular injections within the previous 90 days; lameness associated with neoplasia, primary neurologic disorder, or known immunologic disorder; or surgery on the affected joint in the previous 30 days. The diagnosis of osteoarthritis was based on case history and presentation with the clinical signs of either unilateral or bilateral osteoarthritis (e.g. lameness, morning stiffness, disuse atrophy, decreased range of motion in a joint, joint crepitus, etc.). With regard to age, sex, weight, breed and the severity of the osteoarthritic condition, dogs were well-represented across both treatment groups. Dogs ranged from 10 to 199 lb body weight, and from 1 year to 20

years of age. Dogs were randomly assigned to either carprofen or placebo treatment groups.

iii. Control Drug: Placebo (similar to carprofen formulation except for the omission of the active ingredient).

iv. Dosage Form: The caplets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dosages used: Carprofen: 1 mg/lb given orally twice daily (2 mg/lb divided bid). The duration of therapy was 14 days.
Placebo: 0 mg of carprofen

vii: Test Duration: 28 days

viii. Parameters measured: Pre-treatment (Day 1), interim (Day 4) and post-treatment (Day 15) observations involved a graded lameness evaluation (cumulative score as well as individual values, on a scale of 1 to 5 for lameness, weight bearing, joint mobility, willingness to raise contralateral limb, and pain), with 1 representing minimal lameness and 5 representing severe lameness. Additionally, on Days 2, 4, 8, and 15, owners evaluated response to therapy and the presence or absence of adverse reactions. On or before Day 28, the owner was asked to document the recurrence of the clinical signs and the presence or absence of adverse reactions.

Efficacy was evaluated based on two independent assessments of response: (1) a veterinary evaluation of the overall response to therapy (based on physical evaluation, observation of the gait and mobility, general condition and clinical signs, and a graded lameness evaluation) and (2) an owner evaluation based on the assessment of response to therapy.

Hematology, clinical chemistry, urinalysis, and fecal occult blood analyses were performed prior to treatment, and following treatment.

d. Results: Results of the carprofen and placebo treatments, as evaluated by veterinarians and owners, are provided in Table 2. Progress from Day 1 to Day 15 was assessed as positive or negative on a double blind basis. Improvements were statistically significantly higher among carprofen treated dogs versus placebo based upon both veterinarian (81.3% vs 15.8%, $p < 0.001$) and owner (81.3% vs 25.0%, $p < 0.001$) assessments.

The lameness scores were evaluated in two ways. The first was a comparison of the mean cumulative lameness scores on Day 1 and Day 15, for carprofen and placebo-treated animals, including the change in the mean cumulative score from Day 1 to Day 15. The results are provided in Table 3. No significant difference was detected between carprofen and placebo mean scores on Day 1, but a highly significant difference ($p < 0.001$) was detected between the means on Day 15. Additionally, a highly significant ($p < 0.001$) improvement in the scores of the carprofen treated dogs on Day 15 versus Day 1 was observed as compared to the improvement in the scores of the placebo treated dogs.

The second evaluation analyzed the incidence of improvement from Day 1 to Day 15 for the five individual components as well as the cumulative scores. The results are provided in Table 4. Thirteen dogs were deleted from from these analyses (one receiving carprofen and twelve receiving placebo) because they did not complete the day 15 evaluation, generally due to perceived treatment failure. The incidence of positive change from Day 1 to Day 15 in each of the individual scores as well as for the cumulative score was very significant ($p < 0.001$) for the carprofen treated dogs versus the placebo treated dogs.

Table 2
Percentages of Positive Improvement for the Veterinary and Owner Evaluations

Percent Improvement (Number positive responses/Total number responses)		
	Veterinary Evaluation	Owner Evaluation
Carprofen	81.3 (87/107)	81.3 (87/107)
Placebo	15.8 (19/120)	25.0 (30/120)
P-Value	<0.001	<0. 001

Table 3
Mean Cumulative Lameness Scores

	Day 1	Day 15	Day 1 minus Day 15
Carprofen	12.56	9.52	3.041
Placebo	12.21	11.62	0.137
P-Value	0.537	0.0006	0.0001

Table 4
Percent of Positive Improvement for the Individual
Components and Cumulative Lameness Scores

SCORE	Percent Of Cases Improved (Number improved/Total number)		
	CARPROFEN	PLACEBO	P VALUE
Lameness	56.6 (60/106)	12.0 (13/108)	<0.001
Weight bearing	52.8 (56/106)	8.3 (9/108)	<0.001
Joint Mobility	49.1 (52/106)	9.3 (10/108)	<0.001
Willingness	59.4 (63/106)	9.3 (10/108)	<0.001
Pain	61.3 (65/106)	13.0 (14/108)	<0.001
Cumulative	77.4 (82/106)	17.6 (19/108)	<0.001

Pre-treatment and post-treatment serum alanine aminotransferase (ALT) values varied, with both increases and decreases occurring after treatment in both placebo and carprofen groups. Fifteen dogs in the carprofen group had higher ALT values after treatment compared to pre-treatment values and eight dogs in the placebo group had increases after treatment. Magnitude of the increases were similar in both groups, with the exception of a single dog in the carprofen group, which had an increase in ALT after treatment from 100 IU to 1166 IU.

e. Statistical Analysis: The incidence of positive responses obtained from the veterinarian and owner assessments were compared for total carprofen treated cases versus placebo cases using the Cochran-Mantel-Haenszel procedure (Fleiss, 1984, Statistical Methods for Rates and Proportions, 2nd ed.) for combining evidence from multiple investigators or clinics. The analyses were performed using PROC FREQ in SAS 6.08 (Statistical Analysis System).

With respect to the lameness data, the cumulative lameness scores at Day 1 and Day 15 and the change in scores from Day 1 to Day 15 were analyzed using an Analysis of Variance model, with terms for investigator, treatment and the investigator-by-treatment interaction (PROC GLM SAS 6.08). In addition, the changes in scores from Day 1 to Day 15 for each of the five lameness components as well as cumulative totals were assessed as positive or negative depending upon whether a score improved or remained unchanged/became worse from Day 1 to Day 15. As above, the incidences of positive assessments were compared for carprofen versus placebo dogs using the Cochran-Mantel-Haenszel procedure.

f. Conclusions: In clinical small-animal practice settings, carprofen was shown to be safe and effective in relieving the acute signs associated with a wide variety of osteoarthritic conditions.

g. Adverse Reactions: Adverse reactions to carprofen were not reported. An animal which received ibuprofen following carprofen therapy had evidence of gastrointestinal ulceration. Due to the combination with another NSAID, this condition may not have been related to carprofen.

3. **Rimadyl® (carprofen) clinical trials in a university setting**
(Report No. CR-G-5002-94)

a. Type of Study: Blind, Well-controlled Multicentered Clinical Field Study

b. Investigators:

INVESTIGATOR	CASES
Dr. Steven Budsburg College of Veterinary Medicine University of Georgia Athens, GA	14
Dr. J. Lincoln School of Veterinary Medicine Washington State University Pullman, WA	3
Dr. P. Vasseur School of Veterinary Medicine University of California-Davis Davis, CA	37
Dr. A. Johnson Small Animal Veterinary Clinic University of Illinois Urbana, IL	16
TOTAL	**70**

c. General Design:

i. Purpose: The objective of this study was to determine the safety and efficacy of Rimadyl® (carprofen) for the relief of the acute signs associated with canine osteoarthritis.

ii. Test Animals: Seventy cases were involved in this study. Of the 70 cases, 34 were treated with carprofen while 36 were treated with placebo. Dogs presenting in the course of clinical practice with an osteoarthritic condition clinically manifest as unilateral lameness were admitted to the study. Dogs

were excluded from enrollment if any of the following were present: bilateral lameness; pregnancy; known bleeding disorders; treatment with topical or systemic anti-inflammatory drugs or antibiotics; intra-articular injections within the previous 90 days; lameness associated with neoplasia, primary neurologic disorder, or known immunologic disorder; or surgery on the affected joint in the previous 30 days. The diagnosis of osteoarthritis was based on case history, presentation with the clinical signs of osteoarthritis (e.g. lameness, morning stiffness, disuse atrophy, decreased range of motion in a joint, crepitus, etc.) and radiographic evidence of an osteoarthritic condition. With regard to age, sex, weight, breed and the severity of osteoarthritic condition, dogs were well-represented across both treatment groups. Dogs ranged from 33 to 129 lb body weight, and from less than 1 year (8 months) to 12 years of age. Dogs were randomly assigned to either carprofen or placebo treatment groups.

iii. Control Drug: Placebo (similar to carprofen formula except for the omission of the active ingredient).

iv. Dosage Form: The caplets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dosages used: Carprofen: 1 mg/lb given orally twice daily (2 mg/lb divided bid). The duration of therapy was 14 days.
Placebo: 0 mg of carprofen

vii. Test Duration: 28 days

viii. Parameters Measured: Pre-treatment (Day 1), interim (Day 4) and post-treatment (Day 15) observations involved a graded lameness evaluation (cumulative score as well as individual values, on a scale from 1 to 5, for lameness, weight bearing, joint mobility, willingness to raise contralateral limb, and pain) and force plate evaluation. Additionally, on Days 2, 4, 8, and 15, owners evaluated response to therapy and the presence or absence of adverse reactions. On or before Day 28, the owner was asked to document the recurrence of the clinical signs and the presence or absence of adverse reactions.

Efficacy was evaluated based on three independent assessments of response: (1) a force plate evaluation; (2) a veterinary evaluation of the overall response to therapy (based on physical evaluation, observation of the gait and mobility,

general condition and clinical signs, and a graded lameness evaluation) and (3) an owner evaluation based on the assessment of response to therapy.

Hematology, clinical chemistry, urinalysis, and fecal occult blood analyses were performed prior to treatment, and following treatment.

d. Results: Overall results of the carprofen and placebo treatments, as evaluated by the owner, veterinarian and force plate, are provided in Table 5. The percent of cases showing improvement (Day 15 compared to Day 1) was higher for the carprofen treated dogs than for the placebo treated dogs. In the case of the veterinary ($p = 0.021$) and owner ($p = 0.011$) evaluations, the improvement was statistically significant ($P < 0.05$). The improvement rate as evaluated using the force plate evaluation approaches statistical significance ($p = 0.069$).

The lameness scores were evaluated two ways. The first was a comparison of the mean cumulative lameness scores on Day 1, Day 15 and the change in the mean cumulative score from Day 1 to Day 15 for carprofen and placebo treated animals. The results are provided in Table 6. The second evaluation analyzed the incidence of improvement from Day 1 to Day 15 for the five individual components of the lameness score as well as the cumulative scores. The results are provided in Table 7. In both the evaluations, the results showed numerical improvement with carprofen, but were not found to be statistically significant. There is a hint that carprofen treated dogs may have been somewhat less painful, and therefore, more able to bear weight on the affected limb as evidenced by the higher percentage of dogs (32.4% vs. 19.4%) with improved weight bearing and (41.2% vs. 36.1%) with diminished pain.

Table 5
Percentages of Positive Improvement for the Veterinary,
Owner and Force Plate Evaluations

Percent Improvement (Number Positive Responses/Total Number Responses)			
	Veterinary Evaluation	Owner Evaluation	Force Plate Evaluation
Carprofen	52.9 (18/34)	70.6 (24/34)	79.4 (27/34)
Placebo	25.0 (9/36)	38.9 (14/36)	58.3 (21/36)
P-Value	0.021	0.011	0.069

Table 6
Mean Cumulative Lameness Scores

	Day 1	Day 15	Day 1 minus Day 15
Carprofen	12.98	11.25	1.726
Placebo	12.33	11.72	0.609
P-value	0.517	0.656	0.157

Table 7
Percent of Positive Improvement for the Individual Components
and Cumulative Lameness Scores

Score	Percent Of Cases Improved (Number improved/Total number)		
	CARPROFEN	PLACEBO	P-Value
Lameness	26.5 (9/34)	25.0 (9/36)	0.855
Weight bearing	32.4 (11/34)	19.4 (7/36)	0.209
Joint Mobility	23.5 (8/34)	22.2 (8/36)	0.844
Willingness	26.5 (9/34)	25.0 (9/36)	0.812
Pain	41.2 (14/34)	36.1 (13/36)	0.563
Cumulative	67.6 (23/24)	58.3 (21/36)	0.386

In reference to bloodwork, one dog treated with carprofen and two dogs treated with placebo had increased SGPT (ALT) post-drug. The dog receiving carprofen had an increase of 5X between the pre- and post-drug values. The dogs receiving placebo had a 1.6X and 12.4X increase.

e. Statistical Analysis: The incidences of positive responses obtained from the veterinarian, owner and force plate assessments were compared for all carprofen treated dogs versus placebo dogs using the Cochran-Mantel-Haenszel procedure (Fleiss, 1981, Statistical Methods for Rates and Proportions, 2nd ed.) for combining evidence from various investigators or clinics. The analyses were performed using PROC FREQ in SAS 6.08 (Statistical Analysis System).

With respect to the lameness data, the cumulative lameness scores at Day 1 and Day 15 and the change in scores from Day 1 to Day 15 were analyzed using an Analysis of Variance model, with terms for investigator, treatment and the investigator-by-treatment interaction. In addition, the changes in scores from Day 1 to Day 15 for each of the five lameness components as well as cumulative scores were assessed as positive or negative depending upon whether a score decreased or increased/

remained unchanged from Day 1 to Day 15. As above, the incidences of positive assessments were compared for carprofen versus placebo dogs using the Cochran-Mantel-Haenszel procedure.

f. Conclusions: In clinical university settings, carprofen was shown to be safe and effective in relieving the acute signs associated with canine osteoarthritis.

g. Adverse Reactions: Adverse reactions to carprofen were not reported.

V. ANIMAL SAFETY

A. PIVOTAL STUDIES

1. **A six-week oral safety study with Ro 20-5720/000 (Rimadyl®) in dogs** (Study No. 05966) (Report No. N-127794).

a. Type of Study: Target animal safety and acute toxicity.

b. Investigator: Dr. T. Kirley
Hoffmann-La Roche, Inc.
Nutley, NJ

c. General Design

i. Purpose: The objective of this study was to assess the target animal safety and acute toxicity of carprofen when administered orally twice a day to dogs.

ii. Test Animals: 48 male and female laboratory beagles, 8-13 months of age at study initiation, weighing from 7.1-11.9 kg. Dogs were randomly assigned to six treatment groups (4/sex/group).

iii. Control Drug: Placebo (similar to carprofen formulation except for the omission of the active ingredient).

iv. Dosage Form: The caplets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dosages Used: Test groups are as follows:

Group	Total Daily Dose[a] mg/kg/day	Number of Animals M	F
Control	0	4	4
Control 2[b]	0	4	4
1X	4.4	4	4
3X	13.2	4	4
5X	22.0	4	4
10X[b]	44.0	4	4

a. Doses of 0, 0, 2.2, 6.6, 11 and 22 mg/kg were administered twice daily
b. Interim sacrifice after two weeks of treatment

vii. Test Duration: Six weeks. The control-2 group and the 10X group (22.0 mg/kg BID) were treated for two weeks and then sacrificed.

viii. Parameters Measured:

* Clinical observations
  mortality
  morbidity
  body weight
  food consumption
* Electrocardiography
* Ophthalmoscopy
* Neurological examination
* Laboratory parameters
  hematology
  serum chemistry
  urinalysis
  plasma concentrations of carprofen
  fecal occult blood
* Necropsy, pathology, histopathology

d. Results: All dogs survived to scheduled termination. There were no effects observed on clinical observations, body weights, food consumption, ophthalmologic examination results, neurological examination results, electrocardiographic results, hematologic results, urinalysis results or fecal occult blood examination results.

Serum albumin for a single female dog receiving five times the recommended dose decreased to 2.1g/dL after two weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after four weeks of treatment, and was 2.3 g/dL at the final six week evaluation. Two of eight dogs receiving ten times the recommended dose (10 mg/lb twice daily) for fourteen days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively).

The pre-treatment mean value for AST (SGOT) for dogs in the 10X group was 42.5 IU/L and after two weeks of treatment this value was lower at 40.9 IU/L. The mean AST (SGOT) value for the 10X group after two weeks of therapy was approximately 9 IU/L higher than the control groups. There were no changes noted in serum enzymes indicative of liver pathology.

Black or bloody stools were noted between days 6 to 9 of treatment as follows: one incident in one dog in the 1X group, two incidents in one dog in the 3X group and three incidents in one dog in the 10X group.

At necropsy, there were no effects on organ weights. Redness of the colonic mucosa was observed in one male in the 3X dose group. Five dogs in the 10X group had grossly visible red areas in the intestinal mucosa. Histological examination of these areas revealed no evidence of ulceration in any of these dogs, but did show minimal to moderate congestion of the lamina propria and/or villous atrophy in two of the five dogs treated with 10X the recommended dose of carprofen.

e. Conclusions: Based on this study, the administration of carprofen was not associated with any clinically significant signs of toxicity when given orally at 1, 3 or 5 times the recommended daily dose for 42 consecutive days and at 10 times the recommended dose for fourteen consecutive days. Carprofen was well tolerated and is not expected to produce signs of toxicity when used as directed.

B. CORROBORATIVE STUDIES

1. **One year oral toxicity study of Ro 20-5720 in dogs**
(Report Nos. N-29736 and N-30191).

a. Type of Study: One year oral toxicity

b. Investigator: G.K.S. Roberts, E.A. Pfitzer, and S.E. Sadek
Hoffmann La-Roche

Nutley, NJ

c. General Design

i. Purpose: The purpose of this study was to assess the toxicity of Ro 20-5720 when administered orally once a day by capsule to dogs.

ii. Test Animals: Male and female laboratory beagles, approximately 8 to 14 months old at study initiation, weighing from 7.1 to 12.7 kg.

iii. Control: Empty gelatin capsules

iv. Dosage Form: Gelatin capsules filled with carprofen

v. Route of Administration: Oral

vi. Dosages used: Test groups are outlined below:

Group	Dose (mg/kg/day) once daily	Number of Animals M	F
1	0	9	9
2	2	9	9
3	7	9	9
4	25	9	9

vii. Test Duration: 52 weeks.

viii. Parameters Measured:

* Clinical observations
  - mortality
  - morbidity
  - body weight
  - food consumption
  - general behavior and signs of toxicity
* Neurological examinations
* Ophthalmoscopy
* Laboratory parameters
  - hematology
  - clinical chemistry
  - urinalysis
* Necropsy, pathology, histopathology

d. Results: One dog of the 7 mg/kg/day group died after 40 weeks of treatment. The cause of death could not be established based on the necropsy and histological findings. All other dogs survived the treatment period. After 26 weeks of treatment, 24 dogs (6 dogs per group) were necropsied. All other animals were treated for 52 weeks.

There were no effects on body weight, food consumption, neurology, ophthalmology, hematology, or urinalysis results. The only clinical chemistry changes considered to be related to treatment with carprofen were slight increases in 6/9 males and 1/9 females in ALT values (average increase of approximately 20 IU) in the dogs in the 25 mg/kg/day treatment group.

Scattered episodes of loose stool and emesis were observed. Over the course of the study, the incidence of emesis (total number of episodes) in the control dogs was 0.4% involving 10 dogs; in the low-dose group, 0.8% involving 11 dogs; in the middle-dose group, 0.8% involving 16 dogs; and, in the high-dose group, 1.7% involving 17 dogs. These low incidences of emesis were not considered to be of toxicologic significance.

Minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed. Other gross findings (e.g., gastrointestinal congestion, “pleural white spots”) were noted among both treated and control animals and considered to be of no clinical significance. Histopathological findings (including arteritis, thymic cyst, lymphocytic thyroiditis, salivary adenitis, pancreatic fibrosis, pulmonary inflammation and/or fibrosis, pleural thickening, cerebellar sclerosis, renal calcification, granuloma in the kidney,

foam cells in glomeruli, and hepatic inflammation) were considered incidental and not related to treatment because they were observed rarely and/or in both treated and control animals, although firm conclusions could not be drawn because of a lack of sufficient description of the lesions.

e. Statistical Analysis: Means for each dosed group were compared to the control using Dunnett's two-sided t-test. Standard deviations were compared for each dosed group versus the control using the F-test.

f. Conclusions: Under the conditions of this study, dose levels of 2 and 7 mg/kg/day of Ro 20-5720 were clinically well tolerated by dogs during one year of treatment. At 25 mg/kg/day (approximately 5.7 times the recommended dose) the only clinical change observed, primarily in males, was an elevation of serum L-alanine aminotransferase. There were no gross necropsy or histologic changes that clearly distinguished treated from control dogs after one year of treatment.

2. **Extended-use studies of carprofen in dogs**
(Study No. 2272-8)

a. Type of Study: Non-blinded, multi-centered field study

b. Investigators: Forty-eight investigators in 11 states.

c. General Design:

i. Purpose: To allow for the continued (compassionate) use of carprofen in dogs previously enrolled in clinical efficacy studies and to survey the safety of repeated used.

ii. Test Animals: Two hundred forty-four client-owned dogs with signs of osteoarthritis.

iii. Dosage Form: The caplets administered were the same as the proposed market formulation.

iv. Route of Administration: Oral

v. Dosage Used: 1 mg/lb administered orally twice daily. Animals were allowed 14-day treatment regimens as frequently as their conditions dictated and could discontinue receiving the drug at any time. A re-evaluation by the veterinarian was required prior to the dispensing of each additional fourteen days of therapy.

vi. Test Duration: Animals were enrolled for as little as two weeks, or for as long as five years.

vii. Parameters Measured: Dog owners were requested to evaluate whether an "adverse reaction" had occurred at the end of each 2-week treatment regimen. Such observations were defined as possible adverse events.

d. Results: Two hundred and forty-four dogs received approximately 6561 two-week regimens of carprofen, an average of 26.9 regimens per dog (range 1 to 109). The average duration of participation was 19 months. At the time of study conclusion, 25 dogs were still receiving carprofen.

Possible adverse events were reported in approximately 1.3% of the post-treatment evaluations. It is not possible to determine how many of these reports were related to carprofen treatment, since control drug was not administered. The clinical signs most commonly reported were vomiting, lethargy, decreased appetite, diarrhea and increased appetite. One death, due to unexplained causes in a 20-year-old beagle, was listed as a possible adverse event. However, clinical signs did not relate to known signs of NSAID toxicity.

e. Conclusions: The fact that numerous dogs have been enrolled in this "compassionate" use study for extended periods of time with few complications supports the safety and efficacy of carprofen.

3. **A thirteen week oral toxicity study of Ro 20-5720 in dogs**
(Report No. RCR 24036**)**

a. Type of Study: Thirteen week oral toxicity

b. Investigator: A.C. Levy and S.E. Sadek
Hoffmann La-Roche
Nutley, NJ

c. General Design:

i. Purpose: The purpose of this study was to assess the toxicity of Ro 20-5720 when administered orally once a day by capsule to dogs.

ii. Test Animals: Male and female laboratory beagles, approximately 6 to 8 months old at study initiation, weighing from 7.4 to 11.5 kg.

iii. Control: Empty gelatin capsules

iv. Dosage Form: Gelatin capsules filled with carprofen

v. Route of Administration: Oral

vi. Dosages used: Test groups are outlined below:

Group	Dose (mg/kg/day) once daily	Number of Animals M	F
1	0	3	3
2	1	3	3
3	5	3	3
4	25	3	3

vii. Test Duration: 13 weeks.

viii. Parameters Measured:

* Clinical observations
  - mortality
  - morbidity
  - body weight
  - food consumption
  - general behavior and signs of toxicity
* Neurological examinations
* Ophthalmoscopy
* Laboratory parameters
  - hematology
  - clinical chemistry
  - urinalysis
* Necropsy, pathology, histopathology

d. Results: All dogs survived the 13 weeks of treatment. There were no effects on neurology, ophthalmology, hematology, or urinalysis results. The only clinical chemistry changes considered to be related to treatment were slight increases in ALT values (average increase of approximately 20 IU) in the 25 mg/kg/day treatment as compared to control dogs. There was an unexplainable decrease in body weight of controls during the first 2 weeks of treatment. Body weight gains for treated animals were otherwise comparable to controls. Four females (all among the treated animals) were in estrus, and their uteri weighed more than their non-estrus counterparts. One female receiving 25 mg/kg had reddened jejunal mucosa. Other findings, including prominent Peyers patches, were sporadic among both treated and control animals. Emesis, slight lacrimation of both eyes, and poor appetite were observed sporadically but were not considered significant.

e. Statistical Analysis: Means for each dosed group were compared to the control using Dunnett's two-sided t-test. Standard deviations were compared using the F-test.

f. Conclusions: The oral administration of Ro 20-5720 to dogs by gelatin capsule at doses of 1, 5, and 25 mg/kg/day for 13 weeks was clinically well-tolerated. Laboratory determinations were generally within the ranges expected for untreated dogs except for increases in the values for ALT for 3 dogs in the 25 mg/kg/day dose group. Reddened jejunal mucosa in one female receiving 25 mg/kg/day may have been due to drug administration. Other findings on gross and histological examination were considered infrequent and incidental to treatment, as they occurred among both treated and control animals.

4. Acute toxicity and drug tolerance testing of Ro 20-5720
(Report No. RCR 25760)

a. Type of Study: Increasing dose oral toxicity

b. Investigator: W. Pool and D. Hane
Hoffmann La-Roche
Nutley, NJ

c. General Design

i. Purpose: The purpose of this study was to assess the toxicity of Ro 20-5720 when administered orally to dogs.

ii. Test Animals: Laboratory beagles, 2 male and 1 female, weighing 8.2 to 9 kg.

iii. Dosage form: Gelatin capsules

iv. Route of Administration: Oral

v. Dosages Used: Doubling doses, from 5 mg/kg to 80 mg/kg, were administered as single oral doses on 5 successive days. Two days following the fifth dose, 1 additional dose of 160 mg/kg was administered.

vi. Test Duration: 15 days

vii. Parameters Measured:

- Clinical observations
- Laboratory parameters
  hematology
  clinical chemistry
- Necropsy, pathology, histopathology

d. Results: No clinical signs occurred at the 5 mg/kg dosage. At 10 mg/kg, one dog had loose feces. At 20 mg/kg, 2 dogs had loose feces. At 40 mg/kg, no abnormal signs were observed. At 80 mg/kg, one dog had emesis. No signs were observed on the day of the 160 mg/kg dosing, but on the following day, loose feces were observed in two dogs, and emesis in one of these dogs. Two days and four days following the final dose, one dog vomited and had loose feces. ALT values were elevated following doses of 80 and 160 mg/kg in all three dogs, but returned to normal in two dogs that were tested seven days after dosing was discontinued. Hematocrit and hemoglobin values were lower after 80 and 160 mg/kg doses and seven days after the final dose. All other aspects of hematology and clinical chemistry were normal. One dog was necropsied and hemorrhagic erosions of the small intestines were observed.

e. Conclusions: Under the conditions of this study, brief exposure to doses as high as 160 mg/kg/day of carprofen produced limited clinical signs of toxicity.

VI. HUMAN SAFETY

Human Safety Relative to Food Consumption:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate warning statements relative to user safety.

VII. AGENCY CONCLUSIONS

Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Rimadyl® (carprofen), when used under labeled conditions of use, is safe and effective.

Rimadyl® is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine when a dog has a condition (osteoarthritis) with clinical severity to warrant treatment with such a non-steroidal anti-inflammatory drug.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) of the drug has been approved in any other application.

VIII. LABELING: (attached)

A. Package insert
B. Vial label
C. Box label
D. Shipper label